

Rapid and Spontaneous Synthesis of Schiff Bases Catalyzed by Sulfuric Acid under Environmentally Benign Condition

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ABSTRACT

In the present study, we report the development of an efficient and spontaneous method for the preparation of Schiff bases (C_{1-32}) using H_2SO_4 as catalyst in good to excellent yields. The reaction is spontaneous when it is carried out in sequential manner, that is, to a solution of aldehyde in methanol 2–3 drops of H_2SO_4 were added, to this mixture, a solution of aryl amines was added and shaken for seconds followed by pouring into crushed ice to give solid Schiff bases in good to excellent yields. The Schiff bases synthesized by present method are all known compounds and are characterized by their melting points, IR, and 1H -NMR spectra's. It is noteworthy to state that the present method is accompanied with the procedural simplicity, the efficiency and the easy accessibility of the reaction to give the Schiff bases. We believe that this method will make a remarkable impact on the Schiff base chemistry in the area of environmentally green chemistry.

Key word: Schiff bases, Spontaneous, High yield, Environmentally friendly, Green chemistry.

1. INTRODUCTION

Imines, which are commonly referred to as Schiff bases or azomethines [1], are important for many important organic synthesis [2]. Therefore, imine synthesis processes have lots of significance in organic and pharmaceutical chemistry [3]. Some of the important organic syntheses where imines are used as a component are asymmetric synthesis of α -aminonitriles [4], cycloaddition reactions [5], etc. Imines are also known as biologically significant compound because of their anti-inflammatory nature as well their applicability as anticancer agent [6]. Imines also possess antibacterial and antifungal behavior [7]. Imine synthesis was first reported by Hugo Schiff and since then lots of articles have been published on Imine synthesis. Newer techniques reported for imine synthesis include the use of ionic liquid [8], microwave [9], ultrasound irradiation [10], and so on. Usually, the established equilibrium between the reactant and the product influences the yield of the reaction. Additional interference also appears from water that is produced as by product. These kind of complexities were addressed by the use of dehydrating agents such as P_2O_5/SiO_2 [11], $MgSO_4-Mg(ClO_4)_2$ [12], fuming $TiCl_4$ [13], ammonium chloride [14], copper nitrate [15], and $Mg(ClO_4)_2$ [17-35]. These procedures often involve large quantities of toxic aromatic solvents, longer reaction time, costly reagents, and high temperature. Apart from these, some of these procedures are limited to synthesis of particular type of imines only. The synthesis of Schiff bases is often carried out by acid-catalyzed (CH_3COOH or H_2SO_4) condensation reaction of primary amine and a carbonyl group in an organic solvent. This traditional synthetic method employs the harsh reaction conditions and the use of high boiling point volatile organic solvents such as toluene, which required tedious workup and extensive recrystallization. Because of increased interest in this field, there is a need to develop a convenient, efficient, and practically useful method for the synthesis of Schiff bases. It is surprising to see the literature that the use of sulfuric acid as catalyst for the synthesis of Schiff bases required long reaction time or hazardous reaction conditions, that is,

Nighat Afza and coworkers reported the synthesis of synthesis of Schiff base of 4-chlorobenzaldehyde with 2-amino-5-chloroenzophenone in ethanol catalyzed by H_2SO_4 . The reaction is carried out at $70^\circ C$ for 5 h [36]. Similarly, Roman [37] has reported the synthesis of Schiff base of 4-Amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione by employing the $ArCHO$, ethanol, acid, and reflux for 5 h. Recently, Aispuro-Perez *et al.* [38] have reported the aryl imines under microwave irradiation catalyzed by alumina-sulfuric acid. The Schiff base formation using alumina-sulfuric acid (100 mg) was carried out under microwave by heating at $120^\circ C$ for 10 min. On the other hand, S. Baruah *et al.* [39] have developed H_2SO_4 catalyzed one-pot synthetic methodology for the synthesis of imines under microwave irradiation conditions. Although some of these methods represent a convenient procedure by using H_2SO_4 is reported in different conditions but there is no systematic study is been conducted. In continuation of our efforts to develop the efficient synthetic methodologies for the functional transformation [40-47], herewith, we wish to report an efficient and spontaneous protocol for the preparation of Schiff bases using H_2SO_4 as a catalyst under mild reaction conditions (Scheme 1).

2. EXPERIMENTAL SECTION

2.1 General

All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz for 1H) in

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DMSO-d₆ with tetramethylsilane (TMS) as an internal standard. TLCs were performed on Merck TLC Silica gel 60 F254 plates eluting with EtOAc and developed with iodine. Melting points were determined in glass capillaries on a Mel-Temp 3.0. Mass spectra were measured on Bruker micrOTOF II or maXis (Bruker, Germany) instruments using electrospray ionization (HRESIMS). IR spectrum was recorded on PerkinElmer Infrared spectrophotometer with NaCl.

2.2. General Representative Procedure for the Synthesis of Schiff Bases (C₁₋₃₂)

To the solution of aromatic aldehyde (1 mmol) in 5 ml of methanol taken in a boiling tube was added 2–3 drops of H₂SO₄. To this aromatic amine solution (1 mmol) in 5 ml of methanol made in separate boiling tube was added and shaken for few second (an exothermic reaction is observed as the heat is generated at the surface of the boiling tube).

Spontaneously, the reaction mixture becomes solidified and was immediately poured into crushed ice and stirred for few minutes to get the precipitated product. (In few cases, the precipitation has taken few hours). The precipitate is filtered off on Buchner funnel to get the solid product which was dried over to get the crude product as solid. The crude products (C₁₋₃₂) were recrystallized in methanol to get pure products. The melting point and the spectral data of C₁₋₃₂ are summarized in Tables 1 and 2.

3. RESULTS AND DISCUSSION

While understanding the reaction condition, it is observed that the classical reactions were carried out by mixing the aldehydes, amines, solvent, and acid catalyst at a time and then refluxing for 4–6 h. We understood from the mechanism of this reactions which is seem to

Table 1: Efficient and spontaneous protocol for the synthesis of Schiff bases using H₂SO₄ as a catalyst

Compound	Structure	% yield ^a	M.P-obtained (reported)	Reference ^b
C ₁	R=H; R ₁ =H	92	52–54°C (54°C)	[48]
C ₂	R=H; R ₁ =4-CH ₃	93	113–114°C (114–115°C)	[49]
C ₃	R=H; R ₁ =2-CH ₃	90	39–41°C (40°C)	[50]
	R=H; R ₁ =4-OCH ₃	95	62–63°C (61–62°C)	[51]
C ₅	R=H; R ₁ =4-OH	88	188–190°C (187–192°C)	[52]
C ₆	R=H; R ₁ =2-NO ₂	86	70–71°C (71–73°C)	[53]
C ₇	R=H; R ₁ =3-NO ₂	85	95–96°C (94–97°C)	[53]
C ₈	R=H; R ₁ =4-NO ₂	87	115–116°C (116–117°C)	[53]
C ₉	R=4-Cl; R ₁ =H	90	59–61°C (60–62°C)	[54]
C ₁₀	R=4-Cl; R ₁ =4-CH ₃	91	120–121°C (122°C)	[55]
C ₁₁	R=4-Cl; R ₁ =2-CH ₃	90	39–41°C (42°C)	[50]
C ₁₂	R=4-Cl; R ₁ =4-OCH ₃	93	123–124°C (124–125°C)	[56]
C ₁₃	R=4-Cl; R ₁ =4-OH	88	187–189°C (184–190 °C)	[52]
C ₁₄	R=4-Cl; R ₁ =2-NO ₂	85	77–78°C (78–79°C)	[57]
C ₁₅	R=4-Cl; R ₁ =3-NO ₂	85	121–122°C (121–123°C)	[58]
C ₁₆	R=4-Cl; R ₁ =4-NO ₂	86	140–142°C (140–142°C)	[59]
C ₁₇	R=2-Cl; R ₁ =H	88	65–66°C (64–68°C)	[60]
C ₁₈	R=2-Cl; R ₁ =4-CH ₃	90	52–53°C (52–54°C)	[58]
C ₁₉	R=2-Cl; R ₁ =2-CH ₃	86	77–78°C (77–80°C)	[61]
C ₂₀	R=2-Cl; R ₁ =4-OCH ₃	90	59–61°C (60–62°C)	[58]
C ₂₁	R=2-Cl; R ₁ =4-OH	85	156–157°C (150–159°C)	[52]
C ₂₂	R=2-Cl; R ₁ =2-NO ₂	86	112–114°C (113–115°C)	[62]
C ₂₃	R=2-Cl; R ₁ =3-NO ₂	85	113–115°C (114–116°C)	[63]
C ₂₄	R=2-Cl; R ₁ =4-NO ₂	87	121–122°C (122–123°C)	[58]
C ₂₅	R=4-OH-3-OCH ₃ ; R ₁ =H	92	107–109°C (100–110°C)	[64]
C ₂₆	R=4-OH-3-OCH ₃ ; R ₁ =4-CH ₃	95	119–120°C (118–121°C)	[65]
C ₂₇	R=4-OH-3-OCH ₃ ; R ₁ =2-CH ₃	90	113–114°C (113–114°C)	[50]
C ₂₈	R=4-OH-3-OCH ₃ ; R ₁ =4-OCH ₃	92	134–137°C (134–137°C)	[64]
C ₂₉	R=4-OH-3-OCH ₃ ; R ₁ =4-OH	88	141–142°C (140–143°C)	[64]
C ₃₀	R=4-OH-3-OCH ₃ ; R ₁ =2-NO ₂	86	51–53°C (52–54°C)	[59]
C ₃₁	R=4-OH-3-OCH ₃ ; R ₁ =3-NO ₂	85	130–131°C (132°C)	[66]
C ₃₂	R=4-OH-3-OCH ₃ ; R ₁ =4-NO ₂	88	159–160°C (160–162°C)	[67]

^aAll the Schiff bases prepared in the present study are known products and their corresponding references are given; ^bthe % yields are calculated from isolated products

Table 2: Efficient and spontaneous protocol for the synthesis of Schiff bases using H₂SO₄ as a catalyst-IR and ¹H-NMR characteristic peaks

Compound	Structure	Physical state	IR ν (cm ⁻¹)	¹ H-NMR/(DMSO), δ (ppm)
C ₁	R=H; R ₁ =H	Yellow solid	3049 (Ar, C-H), 1608 (s, C=N), 1530, 1492 (Ar, C-C).	8.45 (s, 1 H), 7.92–7.23 (Ar-H, 10H)
C ₂	R=H; R ₁ =4-CH ₃	White solid	3052 (Ar, C-H), 1615 (s, C=N), 1543, 1486 (Ar, C-C)	8.46 (s, 1H), 7.91–7.12 (Ar-H, 9H), 2.37 (s, 3H)
C ₃	R=H; R ₁ =2-CH ₃	White solid	3037 (Ar, C-H), 1607 (s, C=N), 1527, 1478 (Ar, C-C)	8.54 (s, 1H), 7.91–7.12 (Ar-H, 9H), 2.31 (s, 3H)
C ₄	R=H; R ₁ =4-OCH ₃	Orange solid	3018 (Ar, C-H), 1617 (s, C=N), 1580, 1526 (Ar, C-C)	8.48 (s, 1H), 7.90–6.92 (Ar-H, 9H), 3.83 (s, 3H, OCH ₃)
C ₅	R=H; R ₁ =4-OH	Pale yellow solid	3321 (br, OH), 3110 (Ar, C-H), 1637 (s, C=N), 1890, 1535 (Ar, C-C)	9.58 (s, 1H), 8.08 (s, 1H), 6.78–7.49 (ArH, 9H)
C ₆	R=H; R ₁ =2-NO ₂	Reddish-yellow solid	1595, 1575, 1500 (Ar-C=C-) 2925, (Ar-C-H) 2910 1623, (C=N-) 1456 9 (s NO ₂) and 1338, 1180 (C-N)	8.98 (s, 1H), 7.95–7.45 (ArH, 9H)
C ₇	R=H; R ₁ =3-NO ₂	Yellowish-orange solid	1595, 1585, 1500 (Ar-C=C-), 2925, 2980 (Ar-C-H), 1628 (-C=N-), 1487 (s, -NO ₂), 1356 and 1185 (-C-N)	8.77 (s, 1H), 7.90–7.34 (ArH, 9H)
C ₈	R=H; R ₁ =4-NO ₂	Yellow solid	1590, 1582, 1510 (Ar-C=C-), 3035, 2980 (Ar-C-H), 1622 (-C=N-), 1440 and 1355 (s, -NO ₂) and 1178 (-C-N)	8.92 (s, 1H), 8.21 (s, 1H), 7.48 (ArH, 9H)
C ₉	R=4-Cl; R ₁ =H	Yellow solid	3044 (Ar, C-H), 1620 (s, C=N), 1524, 1498 (Ar, C-C).759 (Ar-Cl)	8.89 (S,1H), 6.50–7.08 (Ar-H,9H)
C ₁₀	R=4-Cl; R ₁ =4-CH ₃	Cream solid	3020 (Ar, C-H), 1594 (s, C=N), 1530, 1492 (Ar, C-C).760(Ar-Cl)	8.45(s, 1H), 7.13–7.82 (m,8H), 2.42 (s, 3H)
C ₁₁	R=4-Cl; R ₁ =2-CH ₃	White solid	2985 (Ar, C-H), 1624 (s, C=N), 1543, 1498 (Ar, C-C).783 (Ar-Cl)	8.25 (s, 1H), 7.21–7.88 (m,8H), 2.28 (s, 3H)
C ₁₂	R=4-Cl; R ₁ =4-OCH ₃	Orange solid	3035 (Ar, C-H), 1625 (s, C=N), 1600, 1576 (Ar, C-C).825 (Ar-Cl)	8.42 (s, 1H), 7.83–6.96 (8H, ArH), 3.87 (s, 3H, OCH ₃)
C ₁₃	R=4-Cl; R ₁ =4-OH	Brown solid	3350 (br, OH), 3120 (Ar, C-H), 1654 (C=N), 1620, 1568 (Ar, C-C) 0.795 (Ar-Cl)	9.57 (s, 1H), 8.60 (s,1H), 7.88–6.85 (8H, ArH)
C ₁₄	R=4-Cl; R ₁ =2-NO ₂	Yellow solid	3065 (Ar, C-H), 1628 (C=N), 1333, 1505 (Ar, C-C). 1376 (NO ₂), 815 (Ar-Cl)	8.83 (s,1H), 8.21–7.21 (8H, ArH)
C ₁₅	R=4-Cl; R ₁ =3-NO ₂	Yellow solid	3038 (Ar, C-H), 1608 (C=N), 1320, 1512 (Ar, C-C). 1378 (NO ₂), 873 (Ar-Cl)	8.47 (s,1H), 8.11–7.50 (8H, ArH)
C ₁₆	R=4-Cl; R ₁ =4-NO ₂	Yellow solid	3080 (Ar, C-H), 1625 (C=N), 1333, 1505 (Ar, C-C). 1376 (NO ₂), 832 (Ar-Cl)	8.84 (s, 1H), 8.20–6.76 (m, 8H)
C ₁₇	R=2-Cl; R ₁ =H	White solid	3021 (Ar, C-H), 1604 (s, C=N), 1508, 1465 (Ar, C-C).774 (Ar-Cl)	8.75 (S,1H), 6.48–7.28 (Ar-H,9H)
C ₁₈	R=2-Cl; R ₁ =4-CH ₃	Yellow solid	3024 (Ar, C-H), 1625 (s, C=N), 1562, 1484 (Ar, C-C), 812 (Ar-Cl)	8.92 (1H, s, CH=N), 8.22–7.23 (8H, m, ArH), 2.38 (3H,s, CH ₃).
C ₁₉	R=2-Cl; R ₁ =2-CH ₃	Yellow solid	2967 (Ar, C-H), 1618 (s, C=N), 1548, 1475 (Ar, C-C), 795 (Ar-Cl)	8.57 (s, 1H), 7.35–7.91 (m,8H), 2.35 (s, 3H)
c ₂₀	R=2-Cl; R ₁ =4-OCH ₃	Orange solid	3045 (Ar, C-H), 1610 (s, C=N), 1621, 1553 (Ar, C-C), 828 (Ar-Cl)	8.95 (s, 1H), 8.22–6.98 (m, 8H), 3.85 (s, 3H,OCH ₃)
c ₂₁	R=2-Cl; R ₁ =4-OH	Brown solid	3315 (br, OH), 3025 (Ar, C-H), 1618 (C=N), 1632, 1588 (Ar, C-C), 818 (Ar-Cl)	9.44 (s, 1H, OH) 8.38 (s, 1H), 6.76–7. 20 (8H)
C ₂₂	R=2-Cl; R ₁ =2-NO ₂	Yellow solid	2987 (Ar, C-H), 1615 (C=N), 1534, 1332 (Ar, C-C). 1365(NO ₂), 868 (Ar-Cl)	8.62 (s,1H), 8.35–7.36 (8H, ArH)
C ₂₃	R=2-Cl; R ₁ =3-NO ₂	Yellow solid	2995 (Ar, C-H), 1612 (C=N), 1528, 1338 (Ar, C-C). 1362 (NO ₂), 856 (Ar-Cl)	8.54 (s,1H), 8.26–7.48 (8H, ArH)
C ₂₄	R=2-Cl; R ₁ =4-NO ₂	Yellow solid	3105, 3073 (Ar, C-H), 1600, (C=N), 1509, (C=C), 1337, 1193 (NO ₂), 1049, 859, 755 (C-Cl).	9.12 (s, 1H), 6.50–7.02 (m, 8H)

(Contd...)

Table 2: (Continued)

Compound	Structure	Physical state	IR ν (cm ⁻¹)	¹ H-NMR / (DMSO), δ (ppm)
C ₂₅	R=4-OH-3-OCH ₃ ; R ₁ =H	Yellow solid	3413 (=C-OH), 3090, 2935 (Ar-C-H), 1585 (-C=N), 1516 1428 (-C=C)	9.44 (OH, 1H), 8.65 (-N=CH, 1H)-, 6.76-7.84 (m, 8H), 3.78 (s, 3H, -OCH ₃)
C ₂₆	R=4-OH-3-OCH ₃ ; R ₁ =4-CH ₃	Yellow solid	3461 (=C-OH), 3086, 2939 (Ar-C-H), 1589 (-C=N), 1522 1432 (-C=C)	13.35 (s, 1H, -OH), 8.93 (s, 1H, -CH=N-), 7.33 -6.91 (m, 7H, Ar-H), 3.94 (s, 3H, -OCH ₃), 2.32 (s, 3H, -CH ₃)
C ₂₇	R=4-OH-3-OCH ₃ ; R ₁ =2-CH ₃	Creamy solid	3552 (=C-OH),, 3001, 2962 2939 (Ar-C-H), 1622 (-C=N), 1586, 1153 (-C=C),	11.78 (O-H, 1H), 9.23 (s, 1H, H-C=N);), 8.44-6.74 (m, 7H, Ar-H), 3.85 (s, 3H, -OCH ₃), 2.28 (s, 3H, -CH ₃)
C ₂₈	R=4-OH-3-OCH ₃ ; R ₁ =4-OCH ₃	Gray solid	3378 (=C-OH), 3044, 2955 (Ar-C-H), 1592 (-C=N), 1506 1434 (-C=C)	11.45 (O-H, 1H), 8.53 (s, 1H, HC=N);), 8.28-6.21 (m, 7H, Ar-H), 4.02 (s, 3H, -OCH ₃), 3.78 (s, 3H, -OCH ₃)
C ₂₉	R=4-OH-3-OCH ₃ ; R ₁ =4-OH	Brown crystal	3248 (=C-OH), 3012, 2922 (Ar-C-H), 1588 (-C=N), 1516 1438 (-C=C)	9.70 (1H, OH), 9.61 (1H, OH) 8.42 s, 1H, HC=N) 7.49-6.85 (m, 7H, Ar-H) 3.83 (s, 3H, -OCH ₃)
C ₃₀	R=4-OH-3-OCH ₃ ; R ₁ =2-NO ₂	White solid	3124 (=C-OH), 3054, 2901 (Ar-C-H), 1592 (-C=N), 1525 (NO ₂), 1518-1460 (-C=C)	9.92 (s, 1H, -OH), 8.32 (s, 1H, HC=N), 8.34-6.74 (m, 7H, Ar-H), 3.82 (s, 3H, -OCH ₃)
C ₃₁	R=4-OH-3-OCH ₃ ; R ₁ =3-NO ₂	Yellow solid	3235 (=C-OH), 3054, 2901 (Ar-C-H), 1624 (-C=N), 1564 (NO ₂), 1523 1458 (-C=C)	9.75 (s, 1H, -OH), 8.55 (s, 1H, HC=N), 8.16-6.54 (m, 7H, Ar-H), 3.92 (s, 3H, -OCH ₃)
C ₃₂	R=4-OH-3-OCH ₃ ; R ₁ =4-NO ₂	Orange solid	3354-3480 (OH), 1628 (1624 (-C=N), 1544, 1342 (NO ₂), 1512 1424 (-C=C)	9.88 (s, 1H, -OH), 8.36 (s, 1H, HC=N), 8.08-6.90 (m, 7H, Ar-H), 3.80 (s, 3H, -OCH ₃)

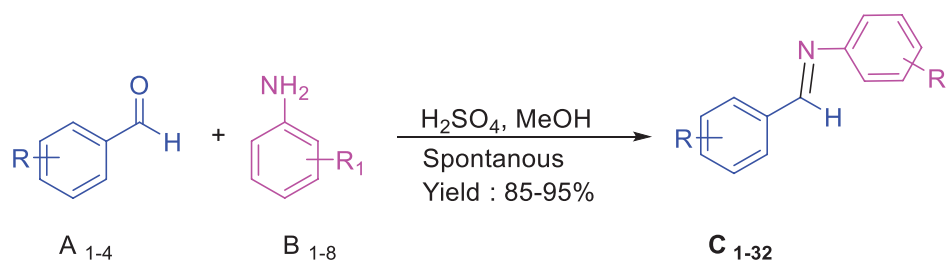
As all the Schiff bases synthesized in the present study are known compounds, the compounds are characterized by IR and ¹H-NMR spectra and the data are in agreement with the literature values

be the activation or the polarization of carbonyl compound and then nucleophilic attack of the amine to the carbonyl carbon followed by dehydration of water to yield the Schiff base. We assume that if the carbonyl group is first protonated with H₂SO₄ to make carbonyl group to be polarized, then addition of the amine solution makes the nucleophilic attack more favorable way. Thus, keeping in the above said points in minds, first, we carried out the reaction as per reported condition in one pot by adding 4-chlorobenzaldehyde, p-toluidine acid, and ethanol as solvent under reflux condition and the reaction is completed in 4-6 h. Then, we modified the reaction condition in terms of sequential addition of the components. First, to the 4-chlorobenzaldehyde solution, 2 or 3 drops of the H₂SO₄ are added to make aldehyde to be protonated and to be polarized, then to this mixture, a solution of p-toluidine is added slowly and shaken for few seconds and then immediately poured into crushed ice. The solid that formed immediately be filtered and crystallized to characterize as Schiff base. Thus, herein, we would like to present the simple and spontaneous procedure for the synthesis of aromatic imines using H₂SO₄ as catalyst (Scheme 1). Although the use of H₂SO₄ as catalyst has been reported in various conditions with long hours of reflux, there are no systematic studies which were carried out. In the present study, we found that the Schiff bases can be synthesized in spontaneously when H₂SO₄ is used as catalyst in methanol as solvent. This present

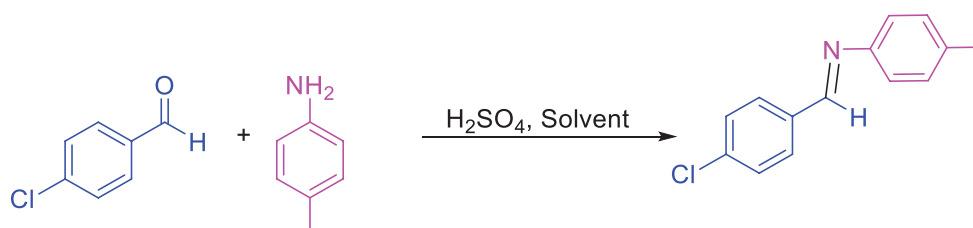
method is useful as it makes the use of inexpensive H₂SO₄ as catalyst with operational simplicity.

To put more insight of the reaction and optimize a feasible procedure, a series of experiments carried out with varying solvents. For optimization of the methodology, we have started the experiment with 4-chlorobenzaldehyde and p-toluidine in equimolar quantities and catalytically amount of various acid catalyst to get the corresponding Schiff base. To identify the effect of the solvent, the reaction was carried out in various solvents such as THF, DCM, EtOAc, toluene, benzene, ethanol, and methanol and it is found that the reaction is more effective when methanol is used as a solvent (Scheme 2; Table 3). Interestingly, it is observed that the reaction under reflux condition proceed smoothly with all the solvents except water with different degree of yield. In the case of water, the reaction did not proceed as the organic aldehydes and amines are not miscible with water hence no reaction is observed and starting materials are obtained back. However when, the present reaction sequence is applied for these solvents it is found that accept ethanol and methanol the reaction did not proceed. In the case of ethanol, the yield is less whereas in the case of methanol yield is high. Thus, the methanol is taken as solvent for further experiments to show the generality of the reaction.

Finally, the optimized condition was obtained when the reaction is carried out in the following sequence, 4-chlorobenzaldehyde in



Scheme 1: Efficient and spontaneous protocol for the synthesis of Schiff bases using H_2SO_4 as a catalyst. (Where: R= H, 4-Cl, 2-Cl and 4-OH-3-OCH₃ (vanillin) and R₁= H, 4-CH₃, 2-CH₃, 4-OCH₃, 4-OH, 2-NO₂, 3-NO₂, 4-NO₂).



Scheme 2: The effect of the solvent in the H_2SO_4 catalyzed Schiff base formation between 4-chlorobenzaldehyde and p-toluidine.

Table 3: The effect of the solvent in the H_2SO_4 catalyzed Schiff base formation between 4-chlorobenzaldehyde and p-toluidine

S. No.	Solvent	Reaction condition	Yield %
1	THF	H_2SO_4 /reflux, 4 h	45
2	THF	H_2SO_4 /shaking for 1 min*	NR
3	DCM	H_2SO_4 /reflux, 4 h	40
4	DCM	H_2SO_4 /shaking for 1 min	NR
5	EtOAc	H_2SO_4 /reflux, 4 h	50
6	EtOAc	H_2SO_4 /shaking for 1 min	NR
7	Toluene	H_2SO_4 /reflux, 4 h	35
8	Toluene	H_2SO_4 /shaking for 1 min	NR
9	Benzene	H_2SO_4 /reflux, 4 h	25
10	Benzene	H_2SO_4 /shaking for 1 min	NR
11	Water	H_2SO_4 /reflux, 4 h	NR as the reactants are not miscible with water
12	Ethanol	H_2SO_4 /reflux, 4 h	65
13	Ethanol	H_2SO_4 /shaking for 1 min	65
14	Methanol	H_2SO_4 /reflux, 4 h	70
15	Methanol	H_2SO_4 /shaking for 1 min	91

*The reaction is carried out using the present sequence reaction, that is, aldehyde+ H_2SO_4 then amine solution addition in the solvent is given in the table

methanol was added 2–3 drops of H_2SO_4 and then in this solution, the p-toluidine in methanol was added and shaken for few seconds. After that, the reaction mixture was immediately poured into crushed ice to obtain the solid product. After optimized conditions were obtained, the generality of the reaction is tested using various substituted aromatic aldehydes and aromatic amines. As all the products are known compounds, they are characterized and confirmed by their melting points, IR, and $^1\text{H-NMR}$ spectra. The products are found to be compiling the literature data (Tables 1 and 2). It is noteworthy

to mention that the present method developed for the Schiff base formation is more advantageous with compare to the classical method of the Schiff base formation using acid catalyst which required heating the reaction mixture for 4–6 h as reported in the literature, whereas in the present method, the reaction is completing spontaneously even in <1 min.

The FTIR spectra of the synthesized Schiff bases C_{1-32} indicated medium intensity band observed in the frequency range 2925–3120 cm^{-1} in all compounds are attributed to $-\text{CH}$ stretching vibrations, namely, symmetric and asymmetric of the aromatic ring. All these compounds showed a characteristic band in the region 1584–1654 cm^{-1} , which is due to $-\text{CH}=\text{N}$ -group (stretching). The three bands in the frequency range 1500–1600 cm^{-1} indicate aromatic nature of the compound. A sharp band in the range 1153–1193 cm^{-1} , in all synthesized Schiff base, may be assigned to the aryl-C-N stretching vibration, additional band at 755–876 cm^{-1} for Schiff base containing chlorine attached to aromatic ring may be attributed to aryl C-Cl group. The Schiff base with group displayed strong band between 1487 and 1564 cm^{-1} and 1337–1365 cm^{-1} is due to nitro group. The $^1\text{H-NMR}$ spectrum of the synthesized Schiff base (C_{1-32}) recorded in DMSO solution shows broad signals between the 9.70 and 13.35 δ corresponds to the OH of the aromatic ring. The singlet peaks between 8.25 and 9.57 δ are due to imine proton of $-\text{CH}=\text{N}$. Aromatic protons appear between 6.48 and 8.44 δ . A singlet at 3.48–4.02 equivalents to 3H represents the OCH_3 protons. Whereas, the singlet's between 2.28 and 2.42 equivalent to three protons represents the methyl protons. Thus, all the compounds are fully characterized and confirmed with their, melting points, IR, and $^1\text{H-NMR}$ spectra and are found to be in agreement with the reported values.

Thus, the above characterization is confirming the formation of the Schiff bases in our present methodology. Thus, the present method for the synthesis of Schiff bases is an advantageous method over the classically reported method of synthesis using H_2SO_4 as catalyst which required long hours of heating 4–6 h under reflux condition. The detail mechanistic studies will be taken as futuristic task of the work.

4. CONCLUSION

We have successfully developed an efficient and spontaneous method for the preparation of Schiff bases (C_{1-32}) using H_2SO_4 as catalyst

in good to excellent yields. It is noteworthy to state that the present method is accompanied with procedural simplicity, the efficiency and the easy accessibility of the reaction to give the Schiff bases.

The sequential addition of the reactant makes this method worthy and we believe that this method will make a remarkable impact on the Schiff base chemistry in the area of environmentally green chemistry.

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6. REFERENCES

1. (a) L. H. Choudhury, T. Parvin, (2011) Recent advances in the chemistry of imine-based multicomponent reactions (MCRs), *Tetrahedron*, **67**(43):8213-8228; (b) T. C. Nugent, M. El-Shazly, (2010) Recent applications of imines as key intermediates in the synthesis of alkaloids and novel nitrogen heterocycles, *Advanced Synthesis and Catalysis*, **352**(5):753-819.
2. W. Qin, S. Long, M. Panunzio, S. Biondi, (2013) Schiff Bases: A short survey on an evergreen chemistry tool. *Molecules*, **18**: 12264-12289.
3. A. Kajal, S. Bala, S. Kamboj, N. Sharma, V. Saini, (2013) Schiff bases: A versatile pharmacophore, *Journal of Catalysts*, **2013**: 1-15.
4. S. Nakamura, N. Sato, M. Sugimoto, T. Toru, (2004) Multi-component reactions: Concepts and applications for design and synthesis, *Tetrahedron Asymmetry*, **15**: 1513-1516.
5. C. Palomo, M. J. Aizpurua, I. Ganboa, M. Oiarbide, (1999) Asymmetric synthesis of lactams by Staudinger ketene-imine cycloaddition reaction, *European Journal of Organic Chemistry*, **6**: 223-235.
6. A. T. Baviskar, U. C. Banerjee, M. Gupta, R. Singh, S. Kumar, M. K. Gupta, S. K. Raut, M. Khullar, S. Singh, R. Kumar, (2013) Synthesis of imine-pyrazolopyrimidinones and their mechanistic interventions on anticancer activity, *Bioorganic and Medicinal Chemistry*, **21**: 5782-5793.
7. M. A. Malik, S. A. Lone, P. Gull, O. A. Dar, M. Y. Wani, A. Ahmad, A. A. Hashmi, (2019) Efficacy of novel schiff base derivatives as antifungal compounds in combination with approved drugs against *Candida albicans*, *Medicinal Chemistry*, **15**: 648-658.
8. W. Sun, C. G. Xia, H. W. Wang, (2003) Synthesis of aziridines from imines and ethyl diazoacetate in room temperature ionic liquids, *Tetrahedron Letters*, **44**: 2409-2411.
9. J. F. Collados, E. Toledano, D. Guijarro, M. Yus, (2012) Microwave assisted solvent-free synthesis of enantiomerically pure n-(tert-butylsulfinyl)imines, *The Journal of Organic Chemistry*, **77**: 5744-5750.
10. K. P. Guzen, A. S. Guarezemini, A. T. G. Orfao, R. Cella, C. M. P. Pereira, H. A. Stefani, (2007) Eco-friendly synthesis of imines by ultrasound irradiation, *Tetrahedron Letters*, **48**: 1845-1848.
11. H. Naeimi, H. Sharghi, F. Salimi, K. Rabiei, (2008) Facile and efficient method for preparation of Schiff bases catalyzed by P₂O₅/SiO₂ under free solvent conditions, *Heteroatom Chemistry*, **19**: 43-47.
12. A. K. Chakraborti, S. Bhagat, S. Rudrawar, (2004) Magnesium perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones, *Tetrahedron Letters*, **45**: 7641-7644.
13. H. Weingarten, J. P. Chupp, W. A. White, (1967) Ketimine syntheses. Use of titanium tetrachloride in a new procedure for their preparation, *The Journal of Organic Chemistry*, **32**: 3246-3249.
14. F. Hossa, A. H. AlShareef, A. H. A. Elhady, M. H. Essam, (2016) Ammonium chloride catalyzed synthesis of novel Schiff bases from spiro[indoline3,4'pyran]3'carbonitriles and evaluation of their antimicrobial and antibreast cancer activities, *SpringerPlus*, **5**: 887.
15. A. Mobinkhaledi, J. S. Peter, P. Matthew, (20029) Rapid and efficient synthesis of schiff bases catalyzed by copper nitrate, *Synthesis and Reactivity in Inorganic, Metal-Organic and Nano-Metal Chemistry*, **39**: 189-192.
16. M. Ferguson, N. Giri, X. Huang, D. Apperley, S. L. James, (2014) One-pot two-step mechanochemical synthesis: Ligand and complex preparation without isolating intermediates, *Green Chemistry*, **16**: 1374-1382.
17. T. Tasneem, R. K. Ravindra, G. Tegginamath, V. B. Bharathi, (2011) An expeditious green synthesis of Schiff bases and azetidinones derivatised with 1,2,4-triazoles, *Journal of Chemical Sciences*, **123**: 657-666.
18. F. H. Westheimer, K. Taguchi, (1971) Catalysis by molecular sieves in the preparation of ketimines and enamines, *Journal of Organic Chemistry*, **36**: 1570-1572.
19. B. E. Love, J. Ren, (1993) Synthesis of sterically hindered imines, *Journal of Organic Chemistry*, **58**: 5556-5557.
20. G. C. Look, M. M. Murphy, D. A. Campbell, M. A. Gallop, (1995) Trimethylorthoformate: A mild and effective dehydrating reagent for solution and solid phase imine formation, *Tetrahedron Letters*, **36**: 2937-2940.
21. R. H. Holm, J. G. W. Everett, A. Chakravorty, (1966) Metal complexes of Schiff bases and α -aminoketones, *Progress in Inorganic Chemistry*, **7**: 83-214.
22. P. A. Vigato, S. Tamburini, (2004) The challenge of cyclic and acyclic Schiff bases and related derivatives, *Coordination Chemistry Reviews*, **248**: 1717-2128.
23. R. W. Layer, (1963) The chemistry of imines, *Chemical Reviews*, **63**: 489-510.
24. A. P. Dobbs, S. Rossiter, (2005) Imines and their N-substituted derivatives: NH, NR, and N-Haloimines. In: R. K. Alan, R. J. K. Taylor, (Eds.), *Comprehensive Organic Functional Group Transformations II*, Oxford, UK: Elsevier, p419-450.
25. R. S. Varma, R. Dahiya, S. Kumar, (1997) Clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation, *Tetrahedron Letters*, **38**: 2039-2042.
26. J. Schmeyers, F. Toda, J. Boy, G. Kaupp, (1998) Quantitative solid solid synthesis of azomethines, *Journal of Chemical Society. Perkin Transactions*, **2**(4): 989-994.
27. A. Vass, J. Dudas, R. S. Varma, (1999) Solvent-free synthesis of N-sulfonylimines using microwave irradiation, *Tetrahedron Letters*, **40**: 4951-4954.
28. K. Tanaka, R. Shiraishi, (2000) Clean and efficient condensation reactions of aldehydes and amines in a water suspension medium, *Green Chemistry*, **2**: 272-273.
29. C. K. Z. Andrade, S. C. S. Takada, L.M. Alves, (2004) Molecular sieves in ionic liquids as an efficient and recyclable medium for the synthesis of imines, *Synlett*, **12**: 2135-2138.
30. M. A. Vazquez, M. Landa, L. Reyes, R. Miranda, J. Tamariz, F. Delgado, (2004) Infrared irradiation: Effective promoter in the formation of N-benzylideneanilines in the absence of solvent,



- Synthetic Communications*, **34**: 2705-2718.
31. M. Gopalakrishnan, P. Sureshkumar, V. Kanagarajan, J. Thanusu, (2007) New environmentally-friendly solvent-free synthesis of imines using calcium oxide under microwave irradiation, *Research on Chemical Intermediates*, **33**: 541-548.
 32. Y. Yuye, (2007) Synthesis of Schiff bases under ultrasound-irradiation. *Asian Journal of Chemistry*, **19**: 2476-2478.
 33. N. Ocal, C. Yolacan, S. Kaban, V. M. Leonor, V. Kouznetsov, (2001) Transformations of schiff bases derived from quinoline-8-carbaldehyde. Synthesis of C-8 substituted quinolines, *Journal of Heterocyclic Chemistry*, **38**: 233-236.
 34. N. Ocal, N. Mor, I. Erden, (2015) Substrate-and base-dependent reactivities of acylketene toward aryl aldimines derived from 2-amino-4-methylpyridine, *Tetrahedron Letters*, **56**: 6468-6471.
 35. B. O. Sucu, N. Ocal, I. Erden, (2015) Direct synthesis of imidazolidin-4-ones via cycloadditions of imines with a Leuchs anhydride, *Tetrahedron Letters*, **56**: 2590-2592.
 36. M. Aslam, I. Anis, N. Afza, R. Mehmood, A. Hussain, T. H. Bokhari, M. T. Hussain, H. Nawaz, M. Khalid. (2015) Synthesis, characterization and antibacterial investigation of divalent metal complexes of NO-donor ligand: {5-chloro-2-[(4-chlorobenzylidene)-amino]phenyl}(phenyl)methanone, *Journal of Saudi Chemical Society*, **19**: 322-326.
 37. G. Roman. (2019) Schiff bases and triazolothiadiazines derived from a thiophene-substituted 4-amino-3-mercapto-1,2,4-triazole, *Acta Chemica Iasi*, **27**: 137-154.
 38. A. Aispuro-Perez, J. Lopez-Avalos, F. Garcia-Paez, J. Montes-Avila, L. A. Picos-Corrales, A. Ochoa-Teran, P. Bastid, S. Montano, L. Calderón-Zamora, U. Osuna-Martinez, J. I. Sarmiento-Sanchez, (2020) Synthesis and molecular docking studies of imines as α -glucosidase and α -amylase inhibitors, *Bioorganic Chemistry*, **94**: 103491.
 39. S. Baruah, A. Fisyuk, I. V. Kulakov, A. Puzari. (2017) An atom economic acid catalyzed synthetic method for aromatic imines, *Asian Journal of Chemistry and Pharmaceutical Sciences*, **2**: 6-9.
 40. A. Kamal, M. Arifuddin, M. V Rao, (1999) Enantioselective ring opening of epoxides with trimethylsilyl azide (TMSN₃) in the presence of β -cyclodextrin: An efficient route to 1,2-azido alcohols, *Tetrahedron Asymmetry*, **10(22)**: 4261-4264.
 41. A. Kamal, M. Arifuddin, M. V. Rao, (2000) Facile and rapid regeneration of carbonyl compounds from their N,N-dimethylhydrazones by employing transition metal complexes, *Synthetic Letters*, **10**: 1482-1484.
 42. A. Kamal, B. A. Kumar, M. Arifuddin, M. Patrick, (2004) An efficient and facile nitration of phenols with nitric acid/zinc chloride under ultrasonic conditions, *Ultrasonics Sonochemistry*, **11**: 455-457.
 43. A. Kamal, S. F. Adil, M. Arifuddin, (2005) Ultrasonic activated efficient method for the cleavage of epoxides with aromatic amines, *Ultrasonics Sonochemistry*, **12**: 429-431.
 44. A. Kamal, S. K. Ahmed, M. Sandbhor, M. N. A. Khan, M. Arifuddin, (2005) Bi(OTf)₃-catalyzed regioselective ring opening of epoxides with phenols: Facile synthesis of 1,3-diaryloxy-2-propanols, *Chemistry Letters*, **34**: 1142-1143.
 45. S. Abdulla, S. Amina, Y. Arun Kumar, M. Arifuddin, K. C. Rajanna, (2011) Mild and efficient nitration of aromatic compounds mediated by transition-metal complexes, *Synthetic Communications*, **41(19)**: 2946-2951.
 46. M. Arifuddin, N. Lakshmikant, N. Rajasekar, D. B. Shinde, (2012) Zinc chloride promoted efficient and facile BOC protection of amines, *Indian Journal of Chemistry, Section B*, **51**: 1168-1172.
 47. K. C. Rajanna, A. Ferdose, K. R. Reddy, M. Arifuddin, M. M. Ali, (2016) Transition metal ions as efficient catalysts for vilsmeier-haack formylation of hydrocarbons with reagents: Kinetics and mechanism, *Journal of Solution Chemistry*, **45**: 371-394.
 48. W. M. Cumming, I. V. Hopper, T. S. Wheeler, (1937) *Systematic Organic Chemistry*, 3rd ed. United States: Sherlock Wheeler, p306.
 49. R. Suresh, D. Kamalakkannan, K. Ranganathan, R. Arulkumar, R. Sundararajan, S. P. Sakthnathan, S. Vijayakumar, K. Sathiyamoorthi, V. Mala, G. Vanangamudi, K. Thirumurthy, P. Mayavel, G. Thirunarayanan, (2013) Solvent-free synthesis, spectral correlations and antimicrobial activities of some aryl imines, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **101**: 239-248.
 50. M. Rai, V. Khera, V. K. Kaul, J. R. Sharma, (2006) Schiff bases of toluidines: Synthesis and effect of position of methyl group on biological potential, *Journal of the Indian Chemical Society*, **83(2)**: 208-209.
 51. A. Djemili, S. Lakrou, Z. Cheraiet, M. Berredjem, N. Aouf, (2015) A simple and highly efficient solvent and catalyst-free synthesis of novel N-sulfamoyl imines, *Green Chemistry Letters and Reviews*, **1**: 48-53.
 52. M. A. Ashraf, K. Mahmood, A. Wajid, (2011) Synthesis, characterization and biological activity of Schiff bases, *International Conferences on Chemistry and Chemical Process*, **10**: 7.
 53. C. J. Patil, M. C. Patil, M. C. Patil, (2018) Studies on synthesis of aldimines: Part-I. synthesis, characterization and biological activity of aldimines from benzaldehyde with variedly substituted anilines, *Recent Research in Science and Technology*, **10**: 23-27.
 54. M. M. Hania, (2009) Synthesis of some imines and investigation of their biological activity, *E-Journal of Chemistry*, **6(3)**: 629-632.
 55. B. Pooja, P. Tanay, (2019) Exploring the utility of glucose as ecofriendly catalyst for microwave assisted green synthesis of Schiff base. *Research Journal of Chemistry and Environment*, **23(2)**: 99-104.
 56. S. Sobhani, F. O. Chahkamali, J. M. Sansano, (2019) A new bifunctional heterogeneous nanocatalyst for one-pot reduction-Schiff base condensation and reduction carbonylation of nitroarenes, *RSC Advances*, **9(3)**: 1362-1372.
 57. E. C. Creencia, M. Kosaka, T. Muramatsu, M. Kobayashi, T. Iizuka, T. Horaguchi, (2009) Microwave-assisted Cadogan reaction for the synthesis of 2-aryl-2H-indazoles, 2-aryl-1H-benzimidazoles, 2-carbonylindoles, carbazole, and phenazine, *Journal of Heterocyclic Chemistry*, **46(6)**: 1309-1317.
 58. M. Kaur, B. Singh, (2014) Synthesis of 4-imino-2H,3H,5H-[1,2,5]thiadiazolidin-1-oxide through cycloaddition reaction of N-sulphonylanilines and N-(α -Cyano- α -aryl)-methylanilines, *Journal of Heterocyclic Chemistry*, **51(4)**: 1157-1161.
 59. Y. M. S. Al-Kahraman, H. M. F. Madkour, D. Ali, M. Yasinzai, (2010) Antileishmanial, antimicrobial and antifungal activities of some new aryl azomethines, *Molecules*, **15(2)**: 660-671.
 60. O. O. Felix, O. E. Regina, A. Ozioma, (2019) Synthesis, characterization and antimicrobial studies of (E)-N-(4-chlorobenzylidene) aniline Schiff base, *International Journal of*

Current Research in Chemistry and Pharmaceutical Sciences, **6(1)**: 16-21.

61. E. E. Elemike, D. C. Onwudiwe, H. U. Nwankwo, E. C. Hosten, (2017) Synthesis, crystal structure, electrochemical and anti-corrosion studies of Schiff base derived from o-toluidine and o-chlorobenzaldehyde, *Journal of Molecular Structure*, **1136**: 253-262.
62. D. Johnston, D. M. Smith, (1976) O-Nitroaniline derivatives. Part VI. Cyanide-induced cyclisation of o-nitroanils. *Journal of the Chemical Society. Perkin Transactions I*, **1976**: 399-400.
63. P. K. Kadaba, (1966) Triazolines-II: Solvent effects on the 1,3-cycloaddition of diazomethane to Schiff bases and the synthesis of 1,5-diaryl-1,2,3-triazolines, *Tetrahedron*, **22**: 2453-2460.
64. S. Chigurupati, (2015) Designing new vanillin schiff bases and their antibacterial studies, *Journal of Medical and Bioengineering*, **4**: 363-366.
65. U. Hasanah, A. Hanapi, R. Ningsih, (2017) Synthesis of Schiff base compound from vanillin and p-toluidine by solvent free-mechanochemical method, *Progress of International Conference on Green Technology*, **8(1)**: 278-281.
66. D. Gebretekle, A. Tadesse, R. K. Upadhyay, A. Dekebo, (2012) Synthesis, characterization and antimicrobial evaluation of some Schiff bases and their thiazolidinone products, *Oriental Journal of Chemistry*, **28(4)**: 1791-1796.
67. J. J. Zainab, M. A. Auribie, (2020) Synthesis and antibacterial activity of Schiff base compounds derived from Glyoxal, Vanillin with their complexes with iron (III), *Egyptian Journal of Chemistry*, **63(10)**: 3985-3994.

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